REMARKS

Applicants have carefully considered the Examiner's Final Office Action, and respectfully request reconsideration of this Application in view of the above amendments and the following remarks.

Pending in this Application are Claims 1-65. Claims 1-63 are withdrawn as belonging to a non-elected invention.

CLAIM REJECTIONS 35 USC §103

The Examiner has rejected Claims 63-65, stating that Applicants' have made an unpersuasive argument that the Qi Reference (Qi et al. Int. J. Hyperthermia 17(1):38-47, 2001) teaches treatment of a cell line, and that it teaches treatment of cells by placing them in the incubator, and that the teachings of the Qi Reference cannot therefore render the current claims obvious.

The Examiner has stated that Applicants' arguments in connection with the Qi Reference pertaining to how *in vitro* applications cannot be extrapolated to *in vivo* applications were unpersuasive because "given the dramatic results obtained by Qi, wherein large numbers of tumor cells were induced to undergo apoptosis following transformation with the p53 gene and heat treatment, one of skill in the art would have been motivated to extrapolate the in vitro results to in vivo tumor treatment. Given the success demonstrated in Qi, one of skill in the art would have had a reasonable expectation of success such in vivo treatment."

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have ***reasonable likelihood of success***, viewed in the light of the prior art. Thus, "obvious-to-try", or "obvious-to-test" or "experiment" is not a proper standard of 35 U.S.C. 103. *In re Goodwin*, 198 U.S.P.Q. 1,3 (C.C.P.A. 1978); *In re Antonie*, 195 U.S.P.Q. 6,8 (C.C.P.A. 1977); *In re Geiger*, 2 U.S.P.Q. 2d 1276, 1278 (Fed. Cir. 1987); *In re Dow Chemical Co.*, 5 U.S.P.Q. 2d 1529, 1532 (Fed. Cir 1988). In fact, the mere need for experimentation to determine parameters needed to make an invention work is an application of the often rejected "obvious-to-try" standard and falls short of the statutory obviousness of 35 U.S.C. 103. The inability of an expert to predict that results obtainable with a claimed product suggests non-obviousness, not

routine experimentation. *Uniroyal Inc. v. Rudkin-Wiely Corp.*, 5 U.S.P.Q. 2d 1434, 1440 (Fed. Cir. 1988).

Applicants submit that the regulatory process required by the United States Food and Drug Administration ("FDA") for new product approval suggests that making the leap from *in vitro* studies to *in vivo* products does not provide a reasonable expectation of success, and is an inventive process without assurance of any particular outcome (See CFR title 21 Parts 1-1499). For example, for an investigational new drug to pass safety for Phase 1 clinical trials, the new drug must pass biodistribution and toxicology studies in at least TWO animal species *in vivo*. *In vitro* results are NOT acceptable. It is commonly known by those of ordinary skill in the art that a successful technique that is used *in vitro*, does not necessarily translate into a technique can be successfully used *in vivo*, or vice versa. For example, it is possible to transfect cells *in vitro* using numerous retroviruses, but the technique does NOT work *in vivo* with direct injections. Applicants submit that the FDA regulatory committee guidelines for a new drug approval show that people in the field do not expect that *in vitro* results can always be extrapolated to *in vivo* models. *In vitro* studies are carried out in an isolated system, with no external influences from other parts of the body. *In vivo* studies are "real world" studies, with many influences from other parts of the body. The two can, and frequently do, result in very different outcomes.

A brochure produced by the Pharmaceutical Researchers and Manufacturers of America (PhRMA Industry Profile, 20007[1]) shows that for every approved drug, approximately 5,000 – 10,000 lead compounds are screened using *in vitro* techniques during the Drug Discovery Phase. The Drug Discovery Phase involves *in vitro* tests for finding a candidate drug for a given target, and assessing toxicity, bioavailability, biodistribution, and metabolic studies, and optimization of a lead compound for higher efficacy or reduced toxicity. Of the 5,000 - 10,000 initial compounds, only about 250 compounds enter the Preclinical Stage, which involves both *in vitro* and animal studies to further assess toxicity, formulation, and manufacturing standards. Of the 250 drugs which appeared promising studies during the Drug Discovery Phase, only about 5 compounds are ever selected for Investigational New Drug Applications and clinical trials in humans, leading to a single approved drug. It is therefore clear that promising results *in vitro* are only a very preliminary step in the drug discovery process, and that *in vitro* results could hardly be said to provide a ***reasonable likelihood of success*** that the compound would be effective,

[1] Accessed at http://www.phrma.org/profiles_%26_reports/ on November 16, 2007, at 11:47am CST.

much less safe, in a human. The *in vitro* activities in a tumor cell line cannot predict host toxicity in an animal. Too many compounds that kill cancer cells *in vitro* are toxic to normal cells in a patient.

A similar dismal statistic is provided by an acquisition document between Glaxo Wellcome, Plc, and SmithKline Beecham, Plc, in New Zealand (Commerce Commission Decision No. 398, ISSN No. 0114-2720 J4097), attached as Exhibit A. This document reports that it takes up to 12 years and NZ$1.1 billion (approximately US$830 million) to develop a medicine, and that on average only one compound out of 10,000 reaches pharmacist's shelves. This supports the above in that, despite extensive *in vitro* testing, drugs which are safe and effective in humans are extremely rare, not having a ***reasonable likelihood of success***.

Applicants submit that the result that the currently claimed material is effective in humans which involves significant inventive step. The invention of Claims 64-65 would not have been obvious to one of skill in the art based on the teaching of Qi Reference, which cannot be said to have a reasonable likelihood of success to be effective and non-toxic in humans. These claims are therefore in condition for allowance.

CONCLUSIONS

Applicants respectfully submit that, in light of the foregoing amendments and comments, Claims 64-65 are in condition for allowance. A Notice of Allowance is therefore requested for all claims. If the Examiner has any other matters which pertain to this Application, the Examiner is encouraged to contact the undersigned to resolve these matters by Examiner's Amendment where possible.

Respectfully submitted,

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